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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,744	04/24/2001	Jorge F. DiMartino	12636-891	5759

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	4

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,744	DIMARTINO, JORGE F.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 16-38* is/are pending in the application.

4a) Of the above claim(s) *3,5,29 and 31-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6-14, 16-28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed on March 12, 2003 (Paper No. 9) under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 1, 3-14 and 16-38 are pending.

Applicants' amendment filed on March 12, 2003 (Paper No. 10) is acknowledged, and applicants' response has been fully considered. Claims 4, 18, 20-22 and 28 have been amended. Claims 3, 5, 29 and 31-38 are non-elected inventions and are withdrawn from consideration. Thus, claims 1, 4, 6-14, 16-28 and 30 are examined.

Objection Withdrawn

3. The previous objection of claims 4 and 28 is withdrawn in view of applicants' amendment to the claim in Paper No. 10.

Rejection Withdrawn

Claim Rejections - 35 USC § 103

4. The previous rejection of claims 1, 4-10, 13, 14, 16-18, 28 and 30 under 35 U.S.C. 103(a) as being unpatentable over Rubinfeld *et al.* (US 2002/0114809 A1) in view of Yang *et al.* (Cancer Research 60, 6890-6894 (December 2000)), is withdrawn in view of applicants' response at page 7 in Paper No. 10.

5. The previous rejection of claims 11 and 12 under 35 U.S.C. 103(a) as being unpatentable over Rubinfeld *et al.* in view of Yang *et al.* as applied to claims 1 and 8 above, further in view of Saito *et al.* (Proc. Natl. Acad. Sci. U.S.A. 96, 4592-4597 (1999)), is withdrawn in view of applicants' response at page 7 in Paper No. 10.

Claim Objections

6. Claim 28 is objected to because the claim recites the term "selected from the group consisting of antibiotic agent". Since there is only one group, antibiotic agent, the term "selected from the group" should be deleted.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1, 4, 6-14, 16-18, 28 and 30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20, 25, 29, 33, 34, 45 and 46 of copending Application No. 09/790,483 (US 2002/0114809 A1, see allowed claims) in view of Zhu *et al.* (Cancer Research 61, 1327-1333 (February 2001) and Saito *et al.* (Proc. Natl. Acad. Sci. U.S.A. 96, 4592-4597 (1999)). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 4, 6-10, 13, 14, 16-18, 28 and 30 in the instant application disclose a method for treating cancer with a combination therapy comprising administering to a patient an effective amount (1-50 mg/m^2 per day) of a DNA methylation inhibitor, in combination with an effective amount of a histone deacetylase inhibitor. This is obvious in view of claims 20, 25, 29, 33, 34, 45 and 46 in the copending

application, which disclose and claim a method of treating a cancer patient comprising administering a therapeutically effective amount (1-20 mg/m^2 per day) of decitabine in combination with an effective amount of an anti-neoplastic agent, wherein the cancer is ovarian, breast, prostate, gastric, lung, pancreas or colon cancer; the reference by Zhu *et al.*, which disclose histone deacetylase (HDA) inhibitors, depsipeptide (FR901228) and trichostatin A, induce apoptotic cell death, and this induced apoptosis is greatly enhanced in the presence of the DNA methyltransferase inhibitor, 5-aza-2'-deoxycytidine (pages 1328-1331); and the reference by Saito *et al.*, which disclose the benzamide derivative MS-27-275 has marked in vivo antitumor activity through HDA inhibition (pages 4594-4595), and also indicate another HDA inhibitor sodium butyrate has been known to arrest the cell cycle and provide various differentiation phenotypes or revertant phenotypes to cancer cells (page 4592), because the DNA methylation inhibitor can enhance the apoptosis induced by the HDA inhibitor, thus the combination therapy suggested by the claims of the copending application and the references would produce the synergic effect of decitabine, a histone deacetylase inhibitor and an anti-neoplastic agent. Both the claims of the instant application and the claims of copending application in view of the references are directed to a method for treating cancer using a combination therapy of a DNA methylation inhibitor and a histone deacetylase inhibitor as well as an anti-neoplastic agent. Thus, claims 1, 4, 6-14, 16-18, 28 and 30 in present application and claims 20, 25, 29, 33, 34, 45 and 46 in the copending application in view of the references are obvious variations of a method for treating cancer using a combination therapy comprising administering an effective amount of decitabine, an effective amount of a histone deacetylase inhibitor and an anti-neoplastic agent to a patient with cancer.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 4, 6-14, 16-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a specific cancer such as breast, lung, stomach or thyroid cancer comprising administering decitabine as a DNA methylation inhibitor in combination with a specific histone deacetylase (HDA) inhibitor such as depsipeptide, phenylbutyrate or arginine butyrate, optionally with an antibiotic agent as an anti-neoplastic agent, does not reasonably provide enablement for a method of treating all cancers with a combination therapy comprising administering a DNA methylation inhibitor in combination with a histone deacetylase inhibitor, optionally with an anti-neoplastic agent, wherein the cancer, the DNA methylation inhibitor, the HDA inhibitor and the anti-neoplastic agent are not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 4, 6-14, 16-28 and 30 encompass a method of treating cancer with a combination therapy comprising administering a DNA methylation inhibitor in combination with a histone deacetylase inhibitor (claims 1, 4, 6-14, 16-27), optionally with an anti-neoplastic agent (claims 28 and 30). The specification, however, only discloses cursory conclusions without data

supporting the findings, which state that the invention provides a method of treating a disease such as cancer using a combination therapy including a DNA methylation inhibitor and a histone deacetylase inhibitor, which triggers cancer cell death through reestablishment of intrinsic death mechanism of cells such as growth arrest, differentiation and apoptosis through activation of genes selectively silenced in cancer cells, and the cancer cells sensitized by such a combination die quickly or become more prone to cell death signals sent by administration of conventional anti-neoplastic agents (page 8, lines 8-18). There are no indicia that the present application enables the full scope in view of a method of treating various cancers using the combination therapy of a DNA methylation inhibitor and a histone deacetylase inhibitor as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding various cancers, DNA methylation inhibitors and histone deacetylase inhibitors, which are not adequately described or demonstrated in the specification.

(2). The absence of working examples:

There are no working examples indicating the claimed methods in association with the variants. The specification has not demonstrated the effect of the combination therapy in the treatment of a specific cancer.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., Zhu *et al.*, Cancer Research 61, 1327-1333 (2001)) indicates histone deacetylase (HDA) inhibitors such as depsipeptide (FR901228) and trichostatin A induce apoptotic cell death, and this induced apoptosis is greatly enhanced in the presence of the DNA methyltransferase inhibitor, 5-aza-2'-deoxycytidine. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific teachings on treating conditions for treating various cancers using a specific DNA methylation inhibitor and a specific histone deacetylase inhibitor and the effect of the combination therapy to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of treating cancer with a combination therapy comprising administering a DNA methylation inhibitor in combination with a histone deacetylase inhibitor, optionally with an anti-neoplastic agent. The specification indicates methylation of DNA or deacetylase of histone plays an important role in regulation of gene expression, and the disease such as cancer is related to aberrant silencing of gene expression, thus, a combination therapy of a DNA methylation inhibitor and a histone deacetylase inhibitor can be used to treat cancer through reestablishment of gene transcription (pages 1, 15-18, 20-21); and further asserts that various cytidine analogs or derivatives can be used as a DNA methylation

inhibitor and various histone deacetylase inhibitors such as hydroxymic acids, cyclic peptides, benzamides, butyrates and depudecin can be used as a histone deacetylase inhibitor (pages 8-9). However, the specification has not demonstrated the effect of the combination therapy although the doses of decitabine, depsipeptide, phenylbutyrate and arginine butyrate have been indicated (pages 11 and 37). Moreover, the specification has not shown the treating conditions such as the dosage, the time, and the frequency of the treatment using various cytidine analogs and histone deacetylase inhibitors other than decitabine, depsipeptide, phenylbutyrate and arginine butyrate in the treatment of a specific cancer. There are no working examples indicating the effect of combination therapy in the claimed method. Since the specification fails to provide sufficient teachings on the treatment of a specific cancer and the effect of using combination therapy, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the combination therapy using a specific DNA methylation inhibitor and a specific histone deacetylase inhibitor.

(5). Predictability or unpredictability of the art:

The claims encompass a method of treating cancer with a combination therapy comprising administering a DNA methylation inhibitor and a histone deacetylase inhibitor, optionally with an anti-neoplastic agent. However, the use of specific inhibitors in the combination therapy, the treating conditions for treating various cancers and the effect of inhibitors are not adequately described in the specification, the invention is highly unpredictable regarding the outcome of the treatment.

(6). Nature of the Invention

The scope of the claims encompasses using combination therapy in the treatment of various cancers, but the specification does not demonstrate the effect of combination therapy using various DNA methylation inhibitors and histone deacetylase inhibitors. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broader than the enabling disclosure. The working examples do not demonstrate the outcome of the treatment, which is unpredictable, and the guidance and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the treatment using various DNA methylation inhibitors and histone deacetylase inhibitors.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 4, 6-14, 16-28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 6-14, 16-28 and 30 are indefinite because the claim lacks an essential step in the method of treating cancer with a combination therapy. The omitted step is the outcome of the treatment. Claims 4, 6-14, 16-28 and 30 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

In response, applicant indicates the rejection under 35 U. S. C. 112, second paragraph, regarding "the claim omits an essential step" is improper because the term is not related to the requirement of definiteness of 112, second paragraph, and the outcome of a method of treatment

does not need to be cited in the claim, when the specification provides guidelines (pages 12-13) as to intended utilities and how the use could be effected (pages 7-8 of the response). The argument is not found persuasive because without recitation of the endpoint of the claimed method, it is not clear whether the treatment would be effective, which is related to the requirement of definiteness of 112, second paragraph. Although the specification indicates the use of combination therapy would reduce potential side effects, which are not cited in the claim, thus, the effectiveness of the treatment is uncertain.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

May 30, 2003

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